[redacted]

P-19-0139

Chemical Name: [redacted]

CASRN: [redacted]

Human Health Report Status:	DATE COMPLETED
HAZARD DRAFT- Pending Review	08/12/2019
HAZARD REVIEWED	08/15/2019
HAZARD FINAL	08/15/2019
RISK DRAFT- pending review	08/23/2019
RISK REVIEWED	10/06/2019
RISK- FINAL- Uploaded	
UPDATE DRAFT	11-16-2021
UPDATE DRAFT REVIEWED	11-18-2021
UPDATE FINAL- Uploaded	11-18-2021

[redacted]

1 HUMAN HEALTH SUMMARY

1.1 Hazard Summary

EPA estimated the human health hazard of this chemical substance based on its estimated physical/chemical properties, by comparing it to structurally analogous chemical substances for which there is information on human health hazard, and other structural information. Absorption of the new chemical substance is expected to be good via all routes based on analogues and physical/chemical properties. For the new chemical substance, EPA identified corrosion to the skin, eyes, and respiratory tract, based on the reactivity of the new chemical substance and acute toxicity, systemic, reproductive, developmental and carcinogenic effects based on analogue data. Surface tension data (OECD 115) were submitted on the new chemical substance and the substance is surface active. EPA identified an inhalation Benchmark Concentration Limit (BMCL) of 0.39 mg/m^3 based on systemic effects , and a LOAEC of 25 mg/m^3 based on portal of entry and systemic effects of an incineration product, and a Benchmark Dose Limit (BMDL) of 0.01 mg/kg/day based on systemic effects of the acid hydrolysis product which are protective for all health effects with the exception of corrosion and were used to derive exposure route- and population-specific points of departure (POD) for quantitative risk assessment. These PODs are protective of all health concerns or effects via the inhalation, oral, or dermal routes. EPA qualitatively evaluated corrosion effects.

1.2 Exposure and Risk Summary

For this assessment, EPA assessed worker exposure via dermal and inhalation exposures. Releases to air were estimated. No releases to water or landfill were expected. Exposure to the general population was assessed via stack and fugitive air inhalation. Exposure to the general population via drinking water, fish ingestion, or groundwater impacted by landfill leachate was not assessed because releases to surface water and landfill are not expected. Consumer exposures were not assessed because consumer uses were not identified as conditions of use.

Risks to human health for the new chemical substance were evaluated using the route-specific effect levels (i.e., BMCL, BMDL, LOAEC). Based on the hazard determination and available quantitative and qualitative risk information, EPA concludes that there is risk for the new chemical substance.

1.2.1 Workers

Risks were identified for workers for bone effects via inhalation exposure based on quantitative hazard data for a hydrolysis product, hydrogen fluoride (MOE = 0.026; Benchmark MOE = 10; Fold Factor = 379).

Risks were identified for workers for systemic effects via inhalation and dermal contract based on quantitative hazard data for analogue (MOE_{Dermal} =0.0005; $MOE_{Inhalation}$= 0.0007; Benchmark MOE = 30; Fold Factor = 40,179).

[redacted]

Skin, eye and respiratory tract corrosion hazards to workers via inhalation and dermal contact were identified based on the hydrogen fluoride hydrolysis product and analogue data. Risks for these endpoints were not quantified due to a lack of dose-response for these hazards.

1.2.2 General Population

Risks were not identified for the general population for systemic effects via inhalation of stack air or fugitive air based on quantitative hazard data for analogue ($MOE_{Stack\ Air}$= 427; $MOE_{Fugitive\ Air}$= 216; Benchmark MOE = 30).

Risks were not identified for the general population for portal-of-entry, liver, kidney, body weight, and neurotoxicity effects via inhalation of stack air based on quantitative hazard data for an incineration product ($MOE_{Stack\ Air}$ = 27,473; Benchmark MOE = 1000).

Skin, eye, and respiratory tract corrosion hazards to the general population are not expected via stack air or fugitive air releases due to dilution of the chemical substance in the media.

Risks were not evaluated for the general population via drinking water, fish ingestion, or ingestion of groundwater impacted by landfill leachate because releases to water and landfill are not expected.

1.2.3 Consumers

Risks to consumer were not evaluated because consumer uses were not identified as conditions of use.

1.3 Assumptions and Uncertainties

- There are no measured data on the new chemical substance.
- Absorption of the new chemical substance is based on physical/chemical properties and analogues.
- The new chemical substance will hydrolyze (sec) to yield hydrofluoric acid and the acid hydrolysis product acetic acid, 2-[difluoro(trifluoromethoxy)methoxy]-2,2-difluoro- (CASRN 39492-88-1).
- Health effects and health evaluation are based on structure, analogue data, hydrolysis products, and potential incineration products.

1.4 Potentially Useful Information

- Specific Target Organ Toxicity
- Pulmonary Effects
- Acute Toxicity
- Skin Irritation/Corrosion
- Serious Eye Damage
- Reproductive Toxicity
- Carcinogenicity

[redacted]

1.5 Hazard Language

Acute Toxicity, Skin Corrosion, Serious Eye Damage, Specific Target Organ Toxicity, Reproductive Toxicity, Carcinogenicity

2 HUMAN HEALTH HAZARD

2.1 Chemistry Summary

PMN: P-19-0139					
		Binding Option Marked:			
		% < 500		% <1000	
			Prop.	Meas.	Est.
			MP		

OECD 115 Surface tension: The surface tension of an aqueous solution of the test item (1 g/L solution) was determined to be [redacted] at 20°C. Determined to be surface active.

2.2 Hazard Summary

2.2.1 Absorption

Absorption of the new chemical substance cannot be estimated, as the new chemical substance will hydrolyze (sec) to yield [redacted] and the acid hydrolysis product a [redacted]

Absorption of the hydrolysis product of the new chemical substance [redacted] is expected to be moderate to good through the skin, good through the GI tract, and poor through the lungs, based on physical/chemical properties.

[redacted]

Absorption of hydrofluoric acid hydrolysis product is expected to be poor to moderate through the skin, nil through the GI tract, and good through lungs, based on physical/chemical properties and analogue data (EU Risk Assessment for [redacted] 2001).

[redacted]

accessed on 3/11/2020.

2.2.2 Structural Alerts

Perfluoro compounds

2.2.3 Human Health Category (From US EPA 2010 document)

Not applicable

2.2.4 OECD QSAR Toolbox

Table for New Chemical Substance and Metabolites (Microbial Metabolism Simulator)

US EPA New Chemical Category	Neutral Organics
Respiratory sensitization alert	No alert found
Protein binding alerts for skin sensitization according to GHS	Skin sensitization Category 1A
Oncologic Primary Classification	Acyl and Benzoyl Type Compounds

2.2.5 Hazard Summary

There are concerns for lung effects (surfactancy) if inhaled based on the surface tension data of the new chemical, however these were not assessed further due to the reactive and corrosive properties of the new chemical substance.

Hazards were identified for acute toxicity (oral, inhalation), serious eye damage, skin irritation, systemic (blood, liver, immune, thyroid), reproductive, developmental, and carcinogenic effects based on data for an analogue of the acid hydrolysis product ([redacted]

There are concerns for corrosion to the skin, eyes, and respiratory tract, based on the reactivity of the new chemical substance.

Based on the hydrolysis product hydrofluoric acid, there are concerns for skeletal fluorosis, neurotoxicity, irritation/corrosion to skin, eyes, and respiratory tract, and systemic effects (liver, kidney, and lung damage). There are also concerns for carcinogenicity based on the reactivity of the acid fluoride and developmental effects based on acid fluorides.

For the potential incineration product of the new chemical substance, there are concerns for portal-of-entry effects (severe signs of irritation in the respiratory tract and eyes, microscopic findings in the upper respiratory tract and lungs), and systemic effects (microscopic findings in the liver and kidneys, body weight loss, and neurotoxicity (changes to neuromuscular excitability and increased body temperature)) based on test data for trifluoroacetic acid (CASRN 76-05-1).

[redacted]

2.3 Toxicity Data

2.3.1 New Chemical Substance Data

2.3.2 None.Analogue/Metabolite Data

2.3.2.1 [redacted]

[redacted]

Health Extractions:

- OECD 471 Bacterial Reverse Mutation Test: Negative with and without activation
- OECD 473 in vitro Mammalian Chromosome Aberration Test: Positive for chromosome aberrations in CHO cells with activation
- OECD 486 Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells in vivo: Negative
- OECD 476 in vitro Mammalian Cell Gene Mutation Tests using the Hprt and xprt genes: negative with and without activation
- OECD 425 Acute Oral Toxicity: Up-and-Down Procedure: Rat (F) oral LD50 550 mg/kg
- OECD 403 Acute Inhalation Toxicity: LD50 >5.2 mg/l
- OECD 402 Acute Dermal Toxicity: LD50 > 5000mg/kg
- Test guideline not specified: Corrosive to skin using the in vitro Corrositex assay;
- OECD 442 Skin Sensitization LLNA: Positive for skin sensitization in mice with EC3 = 37% for [redacted] negative for [redacted]
- ADME data suggest the substance is not metabolized in vivo

Per EPA Office of Water Public Comment Draft Human Health Toxicity Values for [redacted] Acid and Its Ammonium Salt (CASRN 13252-13 and CASRN 62037-80-3):

- Hazards identified include liver, hematological, renal, developmental/reproductive, immune and suggestive evidence of carcinogenic potential.

[redacted]

Table 7. Summary of Study NOAELS/LOAELS

Study	Overall Study Quality (See Appendix B)	Doses (mg/kg/day)	NOAEL or LOAEL (mg/kg/day)	Effects at the LOAEL
28-Day Oral (Gavage) Toxicity Study in Rats (OECD TG 407) DuPont-24447 (2008)	High (≥ 1 and < 1.7)	Males: 0, 0.3, 3, and 30 Females: 0, 3, 30, and 300	NOAEL = 0.3 LOAEL = 3	Hematological effects (↓ RBC count, hemoglobin, and hematocrit in males) Immune effects (↓ globulin and ↑ A/G ratio in males)
28-Day Oral (Gavage) Toxicity Study in Mice (OECD TG 407) DuPont-24459 (2008)	High (≥ 1 and < 1.7)	0, 0.1, 3, and 30	NOAEL = 0.1 LOAEL = 3	Liver effects (single-cell necrosis in males, ↑ relative liver weight in in males, and ↑ hepatocellular hypertrophy in males) Hematological effects (↓ hemoglobin and hematocrit in males) Immune effects (↓ globulin in females, and ↑ A/G ratio in both sexes)
28-Day Oral (Gavage) Immunotoxicity Study in Mice Rushing et al. (2017)	High (≥ 1 and < 1.7)	0, 1, 10, and 100 Note: HFPO dimer acid	NOAEL = 10 LOAEL = 100	Immune effects (TDAR suppression in females, and ↑ lymphocytes in males)
90-Day Oral (Gavage) Toxicity Study in Rats (OECD TG 408) DuPont-17751-1026 (2009)	High (≥ 1 and < 1.7)	Males: 0, 0.1, 10, and 100 Females: 0, 10, 100, and 1,000	NOAEL = 0.1 LOAEL = 10	Hematological effects (↓ RBC count, hemoglobin, and hematocrit in males)
90-Day Oral (Gavage) Toxicity Study in Mice (OECD TG 408) DuPont-18405-1307 (2010)	High (≥ 1 and < 1.7)	0, 0.1, 0.5, and 5	NOAEL = 0.5 LOAEL = 5	Liver effects (↑AST, ALT, and ALP in males; ↑ relative liver weight in males; and ↑ hepatocellular hypertrophy and single-cell necrosis in males)
Combined Chronic Toxicity/ Oncogenicity Study in Rats (OECD TG 453) DuPont-18405-1238 (2013)	High (≥ 1 and < 1.7)	Males: 0, 0.1, 1, and 50 Females: 0, 1, 50, and 500	NOAEL = 1 LOAEL = 50	Liver effects (centrilobular necrosis in both sexes; ↑ ALP, ALT, and SDH in males; and ↑ centrilobular hepatocellular hypertrophy and cystic focal degeneration in males)
Oral (Gavage) Reproduction/ Developmental Toxicity Study in Mice (OECD TG 421; modified according to the Consent Order) DuPont-18405-1037 (2010)	High (≥ 1 and < 1.7)	0, 0.1, 0.5, and 5	NOAEL (F_0) = 0.1 LOAEL (F_0) = 0.5 NOAEL (F_1) = 0.5 LOAEL (F_1) = 5	Liver effects (single-cell necrosis in males, and ↑ relative liver weight in both sexes) Developmental effects (↓ pup weights, and delays in the attainment of balanopreputial separation and vaginal patency)
Prenatal and Developmental Toxicity Study in Rats (OECD TG 414) DuPont-18405-841 (2010)	High (≥ 1 and < 1.7)	0, 10, 100, and 1,000	NOAEL (F_0 and F_1) = 10 LOAEL (F_0 and F_1) = 100	Developmental effects (↑ early deliveries, ↓ fetal weights in both sexes, and ↓ gravid uterine weight)

- OECD TG 421; modified according to the Consent Order: Oral (Gavage) Reproduction/Developmental Toxicity Study in Mice (DuPont-18405-1037 (2010))
  NOAEL (F0) = 0.1 mg/kg-bw/day, LOAEL (F0) = 0.5 mg/kg-bw/day; Liver effects (single-cell necrosis in males, and increased relative liver weight in both sexes)
  NOAEL (F1) = 0.5 mg/kg-bw/day, LOAEL (F1) = 5 mg/kg-bw/day; Developmental effects (decreased pup weights, and delays in the attainment of balanopreputial separation and vaginal patency)

  Crl:CD1(ICR) mice (25/sex/group) were administered the test compound, HFPO dimer acid ammonium salt (purity 84%), by oral gavage (vehicle was deionized water) at doses

[redacted]

of 0, 0.1, 0.5, or 5 mg/kg-bw/day, according to a modified OECD TG 421 (DuPont-18405-1037, 2010; OECD, 2016). The male mice were approximately 6 weeks old and the female mice were approximately 10 weeks old. Parental F0 males were dosed 70 days prior to mating and throughout mating through 1 day prior to scheduled termination, for a total of 84 to 85 total doses. Parental F0 females were dosed for 2 weeks prior to pairing and were dosed through LD 20 for a total of 53 to 65 doses (exceptions include females with no evidence of mating or those that failed to deliver yet were administered a total of 37 to 50 doses). F1 animals (offspring) were dosed daily beginning on PND 21 through PND 40.

In this study, increases in BWs and food consumption were observed at 5 mg/kg-bw/day in F0 animals. In F0 males, increased mean BW gains were reported in the 5 mg/kg-bw/day group during study days 0–49; differences from the control group achieved significance during study days 0–7, 14–21, and 21–28. Significantly higher mean BW gains were observed in this high-dose male group when the overall premating period (study days 0–69) and treatment period (study days 0–84) were evaluated. Mean BW gains were statistically significantly increased in females during both the premating period and throughout gestation at 0.5 and 5 mg/kg-bw/day. At the high dose, mean BW gains were increased (5.1%–14.0%) compared to controls throughout lactation; the differences were significant on LDs 1, 4, and 21. BWs were unaffected at 0.1 and 0.5 mg/kg-bw/day during lactation. Overall, final BW was significantly increased from control by 9% and 14% in males and females administered 5 mg/kg-bw/day, respectively.

An increase in relative kidney weight compared to control by 6.5% was observed only in F0 females at the 5-mg/kg-bw/day. Mild increases in tubular cell hypertrophy were observed in the kidneys of males at greater than or equal to 0.5 mg/kg-bw/day (6/24 mice or 25% and 18/24 mice or 75% of male mice at 0.5 mg/kg-bw/day and 5 mg/kg-bw/day, respectively, compared to 1/25 mice or 4% in the control). Chronic progressive nephropathy was also noted in males at 0.5 mg/kg-bw/day 4/24 mice or 17%) and 5 mg/kg-bw/day (5/24 mice or 21%). This effect was not associated with any evidence of tubular cell degeneration.

Liver effects also were reported in both males and females in this study. In males, mean absolute liver weights were increased 26% and 142% at 0.5 mg/kg-bw/day and 5 mg/kg-bw/day, respectively, as compared to control values. Mean relative liver weights were increased by 26% and 121%, respectively, at the 0.5 and 5 mg/kg-bw/day doses. In females, mean absolute liver weights were increased by 26% and 101% at 0.5 mg/kg-bw/day and 5 mg/kg-bw/day, respectively, as compared to control values. Mean relative (% BW) liver weights were increased by 17% and 80%, respectively. Microscopic findings observed in the liver of F0 males and females administered 0.5–5 mg/kg-bw/day included increases in hepatocellular hypertrophy, single-cell necrosis, mitotic figures, and lipofuscin pigment. F0 females exhibited an increase in the incidence of gross white areas in the liver at 5 mg/kg-bw/day, which correlated with microscopic focal and single-cell necrosis. At doses greater than or equal to 0.5 mg/kg-bw/day, minimal-to-moderate

[redacted]

hepatocellular hypertrophy was observed in both sexes, along with the corresponding increases in relative liver weight outlined above. Specifically, male mice exhibited a 50% and 100% increase in the incidence of hepatocellular hypertrophy compared to control at 0.5 mg/kg-bw/day and 5 mg/kg-bw/day, respectively, and similar increases in incidence was also observed in female mice (58% and 100% at 0.5 mg/kg-bw/day and 5 mg/kg-bw/day, respectively, compared to control). At greater than or equal to 0.5 mg/kg-bw/day, single-cell necrosis of hepatocytes was observed in males. Specifically, single-cell necrosis was observed in 5/24 mice at 0.5 mg/kg-bw/day and 24/24 mice at 5 mg/kg-bw/day mg/kg-bw/day compared to 1/25 mice in the control. Female mice exhibited an increase compared to control in both focal/multifocal necrosis and single-cell necrosis at 5 mg/kg-bw/day . Specifically, 5/24 mice had focal/multifocal necrosis compared to 1/24 in the control and 21/24 mice had single-cell necrosis compared to 1/24 mice in the control. Finally, the incidence of mitotic figures increased in males and females administered 5 mg/kg-bw/day by 75% and 21% compared to control, respectively, while the incidence of lipofuscin pigment increased by 88% and 21% compared to control, respectively.

No treatment-related effects were identified for reproductive parameters (mating, fertility, and copulation indices; mean days between pairing and coitus), although male epidydimal weight relative to final BW was statistically decreased at 5 mg/kg-bw/day in both the left and right testes (12% decrease relative to control). No treatment-related effects were observed for mean gestation length, mean numbers of implantation sites, mean numbers of pups born, live litter size, percentage of males at birth, postnatal survival, or general condition of pups. At 5 mg/kg-bw/day, however, male and female F1 pups exhibited lower mean BWs at PNDs 4, 7, 14, 21, and 28. Male F1 pups continued to exhibit lower mean BWs at PNDs 35 and 40. Although values for the attainment of balanopreputial separation and vaginal patency were within the range of historical control values, the pups showed statistically significant delays in these endpoints at 5 mg/kg-bw/day (a finding that may be related to the observed effects on BW during the preweaning period). Additionally, the day for attainment of vaginal patency did not exhibit a dose-response. The NOAEL (F0) is 0.1 mg/kg-bw/day, and the LOAEL is 0.5 mg/kg-bw/day day based on liver effects (single-cell necrosis in males). The NOAEL (F1) is 0.5 mg/kg-bw/day based on decreased pup BW and delays in attainment of balanopreputial separation and vaginal patency at the high dose.

[redacted]

Table 13. Summary of Determination of POD_{HED}

Endpoint and reference	Species/ Sex	Model	BMR	BMD_{10} (mg/kg/day)	POD (mg/kg/day)	POD Type	DAF	POD_{HED}[a] (mg/kg/day)
HEPATIC								
Constellation of liver lesions in parental males (DuPont-18405-1037, 2010)[b]	Crl:CD1(ICR) mice F_0 parental male	Benchmark dose (ver. 3.1.2) Probit	10%	0.19	0.14	$BMDL_{10}$	0.15	0.02
Constellation of liver lesions in parental females (DuPont-18405-1037, 2010)[b]	Crl:CD1(ICR) mice F_0 parental female	Benchmark dose (ver. 3.1.2) Probit	10%	0.12	0.09	$BMDL_{10}$	0.14	0.01

Notes: N/A = not applicable.
[a] Calculated using $BW^{3/4}$ scaling (EPA, 2011b).
[b] Calculations for DuPont 18405-1037 (2010) rely on pathology conclusions of the NTP PWG (Appendix D)

- POD_{HED} = 0.01 mg/kg/day, the HED based on the $BMDL_{10}$ for liver effects (constellation of liver lesions as defined by the NTP PWG) in parental female mice exposed to HFPO dimer acid ammonium salt by gavage for 53–64 days (DuPont-18405-1037, 2010).
- Total UF = 300, including 10 for UF_H, 3 for UF_A, and 10 for UF_D.

2.3.2.2 [redacted]

[redacted]

- OECD 404 Acute Dermal Irritation/ Corrosion: Skin irritation in rabbits
- OECD 405 Acute Eye Irritation/ Corrosion: Corrosive to rabbit eyes
- OECD 442 Skin Sensitization LLNA: Negative for sensitization
- OECD TG 421 Reproduction/Developmental Toxicity Screening Test (Oral Gavage): Crl:CD1(ICR)Mice 20/sex/dose 0.1, 0.5, and 2.5 mg/kg-day General toxicity in both generations primarily included abdominal distention, changes in body weight, large livers and increased liver weights, and some clinical signs. At the highest dose, three parental males died. EPA considers the value of 0.1 mg/kg-day to be the LOAEL for general toxicity based on increased liver weights seen at 0.1 mg/kg-day; EPA made this decision because the study authors did not evaluate clinical chemistry or histopathology at this dose. Effects seen at 0.1 mg/kg-day related to reduced numbers of implantations and corpora lutea, live litter size, surviving and live pups should be considered as related to treatment because similar effects are seen at higher doses. Although a dose-response is not always apparent, the data show that effects related to survival and litter size are consistent across doses; and thus the Agency considers 0.1 mg/kg-day a LOAEL for reproductive effects.

[redacted]

- OECD 408 90-day oral toxicity study: 10 Crl:CD(SD) rats/sex/dose by gavage 0, 0.02, 0.1, and 0.5 mg/kg bw/day (males) and 0, 0.5, 5, and 50 mg/kg bw/day (females) The LOAEL is 0.1 mg/kg bw/day in males, based on liver cell hypertrophy/necrosis, kidney cell hypertrophy, hematology and clinical chemistry changes; the NOAEL for males is 0.02 mg/kg bw/day. In females, the LOAEL is 5 mg/kg bw/day based on liver and kidney effects and non-statistical increases in enzyme activity, with a NOAEL of 0.5 mg/kg bw/day.

2.3.2.3 [redacted] (data submitted with PMN)

[redacted]

Analogue for Hydrolysis Product:

- OECD 471 Ames assay (S. typhimurium and E. coli): negative with and without metabolic activation

2.3.2.4 [redacted]

[redacted]

Hydrolysis Product

CalEPA Chemical Assessment and Support Document (OEHHA 2008. Technical Supporting Document for Non-cancer RELs, Appendix D3):

- CalEPA has calculated a chronic inhalation reference exposure level (REL) of 0.014 mg/m^3 for hydrogen fluoride based on effects on the bone (skeletal fluorosis) in workers. The value was derived from Derryberry et al. (1963).

  Summary from CalEPA Support Document (pp. 271-272) for Derryberry et al. (1963): The chronic exposure to fluorides, including [redacted] and the incidence of minimal osseous changes were studied in the workplace by Derryberry *et al.* (1963). In this study, the 8-hour time-weighted average fluoride exposure was calculated for the employment period of each of 74 male workers (30 Caucasian, 44 African-American). The overall average fluoride exposure in these workers was measured as a time-weighted average of 2.81 mg F/m^3. In comparison, the 17 workers within this group who had evidence of minimally increased bone density had an average fluoride exposure of 3.38 mg F/m^3. The other workers were exposed to an average measured concentration of 2.64 mg F/m^3. In addition, urinary fluoride levels were greater in the 17 individuals with greatest exposure compared to the remaining 57 workers (average = 5.18 mg F/L vs. 4.53 mg F/L). No differences between exposed and unexposed individuals were observed for gastrointestinal, cardiovascular, or hematologic systems, or in a physical exam. A statistically significant ($p < 0.05$) increase in the incidence of acute respiratory disease as

[redacted]

determined from past medical histories was observed in fluoride-exposed individuals (19/74 vs. 8/67 in controls); radiographic examination revealed a difference of lesser significance ($p < 0.10$) for pulmonary changes (11/74 vs. 4/67). No pulmonary function tests were reported.

An analysis of these data by OEHHA (see derivation section below) showed a statistically significant relationship between air fluoride and the minimal bone density increases. A Pearson correlation matrix of the variables measured in the Derryberry *et al.* study indicated that bone density was best correlated with mean air fluoride level, and to a lesser extent with the age of the individual. A log-logistic regression using the log air fluoride concentration as the independent variable showed a significant ($p < 0.033$) relationship between increasing air fluoride concentrations and probability of skeletal fluorosis. The parameters for the regression were $\beta 0 = -2.3468$ (std. error = 0.6462), and $\beta 1 = 1.1736$ (std error = 0.5508); the odds ratio for the occurrence of skeletal fluorosis was 3.24. Years of exposure were not correlated with increased bone-density, according to a Pearson Correlation procedure ($p = 0.63$). Bone density has been shown to decrease with age after the age of 40 among normal, non-fluoride-exposed males (Runge *et al*., 1979). As expected, age was very highly correlated with years exposed ($p<0.00001$). Therefore including years exposed in the dose-metric likely introduces a confounding variable (see discussion in Section VI.). In addition, Runge *et al*. (1979) found no association between years exposed and mineral content or bone width among 245 aluminum smelter workers exposed to 2.75 or 3.2 mg F/m^3. For these reasons, years exposed were not used as the dose-metric for bone-density in this analysis.

Although a threshold was not readily apparent from the logistic regression model, grouping the 74 individuals by air fluoride exposure level into quintiles of 15 each with one group of 14, allowed for a comparison of group mean responses. The 14 employees exposed to a time-weighted average concentration of 1.07 mg F/m^3 did not exhibit bone density changes. An analysis of the grouped responses using a binomial distribution showed a probability of $p = 0.008$ for obtaining 4/15 increased bone density observations in the 2.34 mg/m^3 group, and a probability of $p = 0.047$ for obtaining 3/15 positive observations in the 1.89 mg F/m^3 group. The 1.89 mg F/m^3 (1.98 mg HF/m^3) group was therefore considered a LOAEC for chronic skeletal fluorosis, and the 1.07 mg/m^3 (1.13 mg HF/m^3) group was considered a NOAEC. The above probabilities assume that a chance occurrence is, at most, 1 in 18 of skeletal fluorosis or other cause leading to an abnormally dense x-ray in the general population. Since osteosclerosis is a rare condition that is associated with several types of hematological malignancies such as myeloid leukemia, the actual incidence of conditions leading to osteosclerosis is far below 1 in 18. This lends strong support to the consideration of 1.89 mg/m^3 as a LOAEC for skeletal fluorosis.

As noted by CalEPA (p. 278), OEHHA's analysis of the data in Derryberry *et al*. (1963) indicates a LOAEC of 1.89 mg/m^3, and a NOAEC of 1.07 mg/m^3. A benchmark concentration (BMC05) of 0.37 mg F/m^3 (0.39 mg HF/m^3) as derived by fitting the probit

[redacted]

model to the log dose in the U.S. EPA's BMDS (version 1.3) software, for the individual mean air exposure data and incidence data.

From p. 278:

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Derryberry *et al.* (1963)
Study population	74 fertilizer plant workers (67 unexposed control subjects)
Exposure method	Occupational
Critical effects	Increased bone density (skeletal fluorosis)
LOAEL	1.89 mg F/m^3 (1.98 mg HF/m^3)
NOAEL	1.07 mg F/m^3 (1.13 mg HF/m^3)
BMC_{05}	0.37 mg F/m^3 (0.39 mg HF/m^3)
Exposure continuity	8 hours/day, 5 days/week
Exposure duration	14.1 years (range = 4.5 to 25.9 years)
Average exposure concentration	0.14 mg HF/m^3 (0.39 x 10/20 x 5/7) or 0.13 mg F/m^3 (0.37 x 10/20 x 5/7)
Human equivalent concentration	0.14 mg HF/m^3 or 0.13 mg F/m^3
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Inhalation reference exposure level for F or HF	0.013 mg F/m^3 (13 µg /m^3; 0.016 ppm; 16 ppb) or 0.014 mg HF/m^3 (14 µg /m^3; 0.017 ppm; 17 ppb)

Reference: Derryberry et al. (1963), as cited in: CalEPA Chemical Assessment

EPA Hydrogen Fluoride Hazard Summary (2016)

- Test Guideline Not Specified Convulsions and irregular heartbeat may occur in humans from ingestion of high doses of fluorides.
- Test Guideline Not Specified Chronic inhalation exposure of humans to low levels of hydrogen fluoride has resulted in irritation and congestion of the nose, throat, and lungs.
- Test Guideline Not Specified Skeletal fluorosis, a bone disease, was reported among workers chronically exposed to fluorides (including hydrogen fluoride) via inhalation.
- Test Guideline Not Specified Damage to the liver, kidneys, and lungs has been observed in animals chronically exposed to hydrogen fluoride by inhalation.

EU Risk Assessment Report for Hydrogen Fluoride (2001)

- Test Guideline Not Specified: 1 h LC50 rats = 792 mg/m3
- Test Guideline Not Specified: 1 hr LC50 mice = 279 mg/m3
- OECD 404: Corrosive to skin of rabbits
- Test Guideline Not Specified: Corrosive to eyes of rabbits
- Test Guideline Not Specified: Ames test: negative
- Test Guideline Not Specified: In vivo chromosomal aberrations: Positive in rats
- Test Guideline Not Specified: 1-month repeated-inhalation (rats): 1 mg HF/m3, 6 hr/day, daily for 1 month; at 1 mg/m3, changes in dental enamel, airways, formation of irregular shaped bone cavities.

[redacted]

- Test Guideline Not Specified: Fertility (rats): 0, 5, 10 mg NaF/kg bw/day for 30 days; LOAEL = 5 mg NaF/kg-bw/day (~2.26 mg F/kg-bw); reduction in fertility, decreased sperm counts and motility, biochemical changes in testes, epididymis, and prostate (Chinoy et al. 1991).
- Test Guideline Not Specified: Fertility study (rabbits): 0, 20, 40 mg NaF/kg bw/day for 30 days; LOAEL = 20 mg NaF/kg-bw/day (~9 mg F/kg-bw); count, biochemical, morphological, numerical, and motility changes in sperm cells. Irreversible loss of fertility (Chinoy et al. 1992).
- Test Guideline Not Specified: Similar to OECD 416 (rats): NOAEL = 250 mg NaF/L; highest dose tested estimated to be about 10 mg F/kg bw/day in adults; no effects observed on fertility.
- Test Guideline Not Specified: Prenatal developmental test: NaF in drinking water at 0, 10, 25, 100, 175, 250 mg NaF/L daily throughout gestation. Groups of females were mated to untreated males. Actual doses were 0.63, 1.76, 7.06, 11.12, 11.35 mg F/kg bw, respectively. Animals received a low fluoride diet, which results in an additional exposure of about 0.6 mg F/kg bw/d. NOAEL for maternal and developmental toxicity = 11.12 mg F/kg bw/day based on slight reduction in corpora lutea and number of implants per dam, increased number of fetuses with skeletal variations.

OECD SIDS SIAP for [redacted], SIAM 10 (2000)

- Sensitization studies with HF are not available. It was agreed that [redacted] and F- are not expected to react with proteins and therefore it is assumed that the substance has no sensitizing properties
- Test Guideline Not Specified: 90-day repeated dose inhalation (rats): Changes in body and organ weights as well as hematological and clinical signs and death were seen at actual concentrations of 7.52 mg/m3; 6 hr/d; 5 d/w for 90 days. This value is equal to a duration corrected value (DCV) of 1340 µg/m3. Based on actual exposure levels a NOAEL of 0.72 mg/m3 is established. Because at higher dose levels apart from irritation also systemic effects occur, a duration corrected equivalent of this NOAEL is calculated. This duration corrected value (NOAEL) amounts to 128 µg/m3. [also reported in EU Risk assessment, Placke and Griffin 1991)
- Test Guideline Not Specified: In epidemiological studies with workers exposed to 0.48 mg total fluoride/m3 (of which 0.2 mg gaseous fluoride) no fluorosis was observed. This level can be considered as an inhalatory NOAEL for fluoride in humans. At this level slight respiratory effects were observed, but these effects were not attributable to [redacted] because simultaneously, exposure to other air-way irritants occurred.

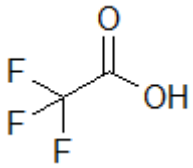
[redacted]

- A study by [redacted] found a U-shaped pattern for the prevalence of overall bone fractures and the level of fluoride in the drinking water of six communities in rural China. The prevalence of bone fractures (adjusted for age and gender) was

[redacted]

significantly elevated in the communities with 0.25–0.34 ppm fluoride (7.41%) or 4.32–7.97 ppm fluoride (7.40%), as compared to the prevalence (5.11%) in the community with 1.00–1.06 ppm fluoride in the water. When only hip fractures since age 20 years were examined, the age- and body mass index (BMI)-adjusted prevalence was only significantly higher in the 4.32–7.97 ppm group; prevalence of 1.20% compared to 0.37% in the 1.00–1.06 ppm group. A similar pattern was found for overall fractures since age of 50 years; the age-adjusted prevalences were 4.80 and 3.28% in the 4.32–7.97 and 1.00–1.06 ppm groups, respectively. The [redacted] study identified a NOAEL of 2.62–3.56 ppm (0.15 mg fluoride/kg/day) and LOAEL of 4.32–7.97 ppm (0.25 mg fluoride/kg/day). The selected value was the basis for derivation of the ATSDR oral MRL [redacted]

2.3.2.5 Trifluoroacetic acid (TFA), CASRN 76-05-1



Incineration Product

ECHA Registered Substances Database

- OECD 403 - acute inhalation toxicity: TFA induced no mortality at the tested concentrations (up to 300 mg/m^3). At the highest concentration, TFA induced local irritation of the nasal cavity epithelium of the rats. This effect was considered reversible since irritation was not noted in the nasal cavity at necropsy at the end of the observation period. The NOAEC for local effects was 300 mg/m^3.
- Skin and eye irritation/corrosion: Corrosive
- OECD 429: Not sensitizing
- OECD 408: Sodium trifluoroacetate was administered continuously via dietary administration to Wistar rats (10/sex/group) at concentrations of 0, 160, 1,600 or 16,000 ppm (equating approximately to 0, 8.4, 82.3, or 876 mg TFA/kg body weight/day in males and 0, 10.1, 103.3, or 1,021 mg TFA/kg body weight/day in females), for at least 90 days. At necropsy a reduction in mean body weight gain of 17% and 6% was observed for males and females, respectively at 16,000 ppm when compared to the controls. Clinical pathology determinations revealed lower mean hemoglobin concentration in females. This slight change was associated with a statistically significantly lower mean corpuscular volume, mean corpuscular hemoglobin and hematocrit. In addition, mean total bilirubin and glucose concentrations were markedly lower in both sexes. Mean values for alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase activities were higher in males. At urinalysis, higher ketone levels were noted in both sexes. Microscopic examination revealed test item related changes in the liver. In all males and most females at 16,000 ppm and several males at 1,600 ppm, a minimal to moderate diffuse centrilobular to panlobular hepatocellular hypertrophy with groundglass appearance of the hepatocellular cytoplasm was

[redacted]

observed. This change was associated with a loss of the periportal hepatocellular vacuolation observed at 16,000 ppm in both sexes and at 1600 ppm in males. The effect was dose-related and correlated with the higher mean liver weight noted in these groups (+33% and +28% relative to vehicle controls in the 16,000 ppm males and females, respectively). There was also a higher incidence of hepatocellular necrotic foci in males at 16,000 ppm when compared to controls, which was considered to be adverse. This finding was correlated with higher individual values of aspartate aminotransferase and alanine aminotransferase activities observed in clinical chemistry evaluation. The dose level of 160 ppm of sodium trifluoroacetate is considered to be a NOAEL in both sexes (equating to 8.4 mg TFA/kg body weight/day in males and 10.1 mg TFA/kg body weight/day in females).

- Test Guideline Not Specified - Subchronic inhalation study: Rats and guinea pigs were exposed to a mixture of vapors and aerosols of trifluoroacetic acid (concentrations comprised between 0.025 and 0.05 mg/L or 0.4 and 0.7 mg/L). The animals were exposed for 4 hrs per day (six days per week) for a period of 5 (rats) or 4 (guinea pigs) months. There were no mortalities. Exposed animals showed severe signs of irritation of the respiratory pathway and of the eyes (reflected in the anxiety of the animals, breathholding, lachrymation, hyperaemia of the conjunctiva, and sanious and sanious-suppurative nasal discharge). There were also effects in the liver and kidney and the animals displayed a body weight loss. A reduction in the neuromuscular excitability was observed in the second month of exposure. By the end of the period of the administration, the neuromuscular excitability of the animals had increased. An increase in body temperature of 1.5 to 2°C was reported. Treatment-related microscopic findings were observed in the upper respiratory pathways (rhinitis, tracheitis, bronchitis) and lungs (thickening of the alveolar septa, peribronchitis, emphysema, pulmonary collapse). In addition, there was dystrophy of the liver and kidneys. A NOAEC was not observed.
- OECD 414 - Prenatal developmental toxicity study: Mated females were administered trifluoroacetic acid by oral gavage at dose levels of 0, 37.5, 75, and 150 mg/kg/day from gestation day 6 to 19. On GD 20, all the surviving study animals were necropsied and examined macroscopically. All females survived until termination and dosing was well-tolerated. There were no adverse effects on body weight, body weight gain, food consumption, pregnancy, cesarean parameters, fetal, placental, and uterine weights, organ weights, or fetal abnormalities, variations or ossification parameters. The NOAEL for maternal and embryo-fetal development toxicity in rats was considered to be 150 mg/kg/day. Due to the non-adverse, test article-related organ weight increases, the maternal and embryo-fetal no-observed-effect-levels NOEL were 75 mg/kg/day (maternal) and 150 mg/kg/day (embryo-fetal).

2.3.3 SDS Data

The SDS appears relevant to the new chemical substance. The CASRNs are identical.

SECTION 2. HAZARDS IDENTIFICATION

GHS classification in accordance with 29 CFR 1910.1200

Acute toxicity (Oral) : Category 3

Acute toxicity (Inhalation) : Category 1

GHS label elements

Hazard pictograms :

Signal Word : Danger

Hazard Statements : H301 Toxic if swallowed.
H330 Fatal if inhaled.

Precautionary Statements :

Prevention:

P260 Do not breathe mist or vapors.
P264 Wash skin thoroughly after handling.
P270 Do not eat, drink or smoke when using this product.
P271 Use only outdoors or in a well-ventilated area.
P284 Wear respiratory protection.

Response:

P301 + P310 + P330 IF SWALLOWED: Immediately call a POISON CENTER/doctor. Rinse mouth.
P304 + P340 + P310 IF INHALED: Remove person to fresh air and keep comfortable for breathing. Immediately call a POISON CENTER/doctor.

Storage:

P405 Store locked up.

Disposal:

P501 Dispose of contents/ container to an approved waste disposal plant.

Other hazards

None known.

[redacted]

SECTION 3. COMPOSITION/INFORMATION ON INGREDIENTS

Substance / Mixture : Substance

Substance name [redacted]

CAS-No.

Components

[redacted]

Actual concentration is withheld as a trade secret

SECTION 11. TOXICOLOGICAL INFORMATION

Information on likely routes of exposure

Inhalation
Skin contact
Ingestion
Eye contact

Acute toxicity

Toxic if swallowed.
Fatal if inhaled.

Product:

Acute oral toxicity	:	Acute toxicity estimate: 167 mg/kg Method: Calculation method
Acute inhalation toxicity	:	Acute toxicity estimate: 62 ppm Exposure time: 4 h Test atmosphere: gas Method: Calculation method

Components:

[redacted]

Acute oral toxicity	:	LD50 (Rat): 167 mg/kg Method: OECD Test Guideline 401
Acute inhalation toxicity	:	LC50 (Rat): 62 ppm Exposure time: 4 h Test atmosphere: gas Method: OECD Test Guideline 403

2.3.4 Other Information

The substance will hydrolyze (sec) to yield hydrofluoric acid and the acid hydrolysis product propanoic acid, 2-[2-[difluoro(trifluoromethoxy)methoxy]-1,1,2,2-tetrafluoroethoxy]-2,3,3,3-tetrafluoro-.

Hydrolysis of the acid fluoride:

[redacted]

Calculations for maximum % release of hydrolysis products:
100 * (MW of hydrolysis product * maximum # groups released from new chemical substance) /MW of new chemical substance

[redacted] 100 * (20 * 1)/414 = 4.83%

2.4 Exposure Routes of Interest

Route of Interest	
X	Inhalation
X	Dermal
X	Ingestion

2.5 Point of Departure (POD) Selected and Basis

2.5.1 POD for Non-Cancer Effects, Inhalation Exposures (4.83% of new chemical substance , Workers Only)

Type: BMCL
Value: 0.39 mg [redacted]/m^3
Chemical: [redacted] (CASRN 7664-39-3)
Route: Inhalation
Study Type: Occupational study in workers
Hazard Endpoint: Systemic (bone) effects
Selection Rationale: Multiple candidate values were identified from studies for analogues of the new chemical substance and identified potential hazards, including acute toxicity (mortality), neurotoxicity, and systemic, reproductive, and developmental effects. A BMCL of 0.39 mg HF/m^3 was identified for bone effects and was selected as the POD value. The selected value was based on bone effects (skeletal fluorosis) and was selected because it is protective for acute toxicity (mortality), neurotoxicity, and systemic, reproductive, and developmental effects. Irritation/corrosion and genotoxicity effects were evaluated qualitatively.
Study details: 8 hours/day, 5 days/week; 74 fluoride-exposed fertilizer plant workers and 67 unexposed control subjects; BMCL is based on increased bone density (skeletal fluorosis), which was considered the critical effect. The BMCL was derived by OEHHA (2008), based on a LOAEC of 1.89 mg F/m^3 (1.98 mg HF/m^3) group for chronic skeletal fluorosis and a NOAEC of 1.07

[redacted] mg/m^3 (1.13 mg [redacted]/m^3) An increase in the incidence of acute respiratory disease was also observed in exposed workers.

Benchmark MOE: 10 (10x for intraspecies)

Reference: Derryberry et al. (1963), as cited in: CalEPA Chemical Assessment (https://oehha.ca.gov/chemicals/hydrogen-fluoride, accessed on 3/11/2020) and Support Document (OEHHA 2008. Technical Supporting Document for Noncancer RELs, Appendix D3)

Derryberry OM, Bartholomew MD, and Fleming RBL. 1963. Fluoride exposure and worker health - The health status of workers in a fertilizer manufacturing plant in relation to fluoride exposure. Arch. Environ. Health 6:503-51.

2.5.2 POD for Non-Cancer Effects via Oral, Inhalation, and Dermal Exposures

Type: BMDL

Value: 0.01 mg/kg/day

Chemical: [redacted]

Route: Oral

Study Type: OECD 421 Reproductive/developmental study

Hazard Endpoint: Systemic (liver) effects

Selection Rationale: Multiple candidate values were identified from analogues and identified potential hazards including systemic, reproductive, and developmental effects. EPA identified a BMDL of 0.01 mg/kg/day based on liver effects, which is the selected POD for the OW EPA draft on GenX chemicals, an analogue of the new chemical substance. Liver effects were observed at the lowest tested dose with another analogue, [redacted] Liver effects for perfluoroethers are observed at doses as low as 0.5 mg/kg-day. Due to the uncertainty regarding the MOA, GenX was selected as the basis for the POD. This POD is protective for all health concerns following oral exposures. No repeated-dose toxicological studies were available for the analogue by the dermal or inhalation routes; however, EPA concluded that route-to-route extrapolations (i.e. oral to dermal and oral to inhalation) were acceptable based on the following considerations and assumptions. First, absorption of the new chemical substance is expected to be good (>60%) through the skin, GI tract, and lungs (see Section 2.2.1). Second, EPA assumed that systemic delivery of the new chemical substance occurs at a similar rate from dermal and inhalation exposures compared to GenX in the reproductive/developmental oral toxicity study. These assumptions were based on: (1) oral administration of the analogue in the reproductive/developmental study and (2) absorption for each route based upon and physical/chemical properties and analogues of the new chemical substance. Therefore, EPA assumed that the POD derived from the reproductive/developmental study would be sufficiently conservative for quantifying risks based on these route-to-route extrapolations.

Benchmark MOE: 30 (10x for intraspecies variability, 3x for intraspecies)

Reference: EPA Office of Water Public Comment Draft Human Health Toxicity Values for [redacted] Dimer Acid and Its Ammonium Salt (CASRN 13252-13 and CASRN 62037-80-3)

[redacted]

2.5.3 POD for Non-Cancer Effects via Inhalation Exposures for Incineration Product (General Population, Stack Air)

Type: LOAEC
Value: 25 mg/m^3
Chemical: Trifluoroacetic acid, CASRN 76-05-1
Route: Inhalation
Study Type: Subchronic inhalation toxicity study; 4 hr/day, 6 days/week, for 5 months (rats) or 4 months (guinea pigs)
Hazard Endpoint: Portal-of-entry effects, systemic (liver, neurological, kidney) effects
Selection Rationale: This POD is expected to be protective of all effects following inhalation exposure to trifluoroacetic acid for the general population via stack air inhalation.
Benchmark MOE: 1000 (10x interspecies, 10x intra-species, 10x LOAEC to NOAEC)
Reference: ECHA Registered Substances Database (accessed on 5/22/2020)

[redacted]

3 HUMAN HEALTH RISK

3.1 USES and EXPOSURES

3.1.1 Uses

Intended use: [redacted] chemical intermediate, [redacted]

3.1[redacted]e

Per Engineering Report dated 07-17-2020

3.1.2.1 Inhalation

[redacted]: Batch

[redacted]

Exposure to Vapor (volatile) (Class II)
Upper Bound PDR: [redacted] mg/day over [redacted] days/yr
Upper Bound LADD: [redacted] mg/kg-day over [redacted] days/yr

[redacted]

Exposure to Vapor (volatile) (Class II)
Upper Bound PDR: [redacted] mg/day over [redacted] days/yr
Upper Bound LADD: [redacted] mg/kg-day over [redacted] days/yr

[redacted]

Exposure to Vapor (volatile) (Class II)
Upper Bound PDR: [redacted] mg/day over [redacted] days/yr
Upper Bound LADD: [redacted] mg/kg-day over [redacted] days/yr

3.1.2.2 Dermal

MFG: Batch

[redacted]

Exposure to Liquid at [redacted]% concentration
High End PDR: 1.1E+3 mg/day over 6 days/yr
High End LADD: 1.2E-1 mg/kg-day over 6 days/yr

[redacted]

Exposure to Liquid at [redacted] concentration
High End PDR: [redacted] mg/day over [redacted] days/yr
High End LADD: [redacted] mg/kg-day over [redacted] days/yr

[redacted]

Equipment Cleaning Losses of Liquids from Multiple Vessels
Exposure to Liquid at [redacted] concentration
High End PDR: [redacted] mg/day over 3 days/yr

[redacted]

High End LADD: [redacted] kg-day over [redacted] days/yr

3.1.3 General Population Exposure

Per Exposure Report dated 07-20-2020

Exposure Scenario[1]	Water						Landfill	Stack Air		Fugitive Air	
Release activity(ies)[2]; exposure calculation(s)[3]	Drinking Water		Fish Ingestion		7Q10[4] CC = 153	PDM Days Exceeded	LADD	ADR (24-hr conc.)	LADD (Annual conc.)	ADR (24-hr conc.)	LADD (Annual conc.)
	ADR	LADD	ADR	LADD							
	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	µg/l	# Days	mg/kg/day	mg/kg/day (µg/m^3)	mg/kg/day (µg/m^3)	mg/kg/day (µg/m^3)	mg/kg/day (µg/m^3)
MFG/USE:Max ADR	--	--	--	--	--	--	--	[redacted]	-- (--)	[redacted]	-- (--)
MFG/USE:Max LADD	--	--	--	--	--	--	--	-- (--)	[redacted]	-- (--)	[redacted]

3.1.3.1 Drinking Water

Not released to surface water

3.1.3.2 Fish

Not released to surface water

3.1.3.3 Landfill

No releases to landfill

3.1.3.4 Air/Inhalation

Stack: ADR as high as [redacted] mg/kg/day ([redacted] µg/m^3) and LADD as high as [redacted] mg/kg/day [redacted] +4 µg/m^3)

Fugitive: ADR as high as [redacted] mg/kg/day ([redacted] µg/m^3) and LADD as high as [redacted] mg/kg/day ([redacted])

3.1.4 Consumer Exposure

No identified consumer exposures

3.2 RISK CALCULATIONS

3.2.1 Worker Calculations

Worker Margin of Exposure (MOE) Calculations using Animal Inhalation POD and Engineering Report PDR

	Animal or Human POD			Worker Exposure				Human Breathing Rates						Benchmark MOE	Endpoint Type
Exposure Route	POD Conc. mg/m^3	POD Period hrs/day	POD Frequency days/wk	Exposure mg/day Potential Dose Rate (PDR)	Total Worker Breathing Volume for PDR Exposure Period m^3	Worker Exposure Duration Hours/Day	Exposure Frequency Days/Wk	Default	Worker	Structural Alert as % of PMN	POD Conc - Duration & Breathing Rate Correction Scenario$_{HEC}$ mg/m^3	Exposure TWA mg/m^3	**Margin of Exposure MOE**	10	BMCL
Inhalation	0.39	8.00	5	[redacted]	10.0	8.00	5	4.90	10.00	4.83%	1.9E-01	1.5E+02	**0.026377**	Fold Factor =	379

[redacted]

Risks were identified for workers for systemic effects via inhalation exposure based on quantitative hazard data for a hydrolysis product (MOE = 0.026; Benchmark MOE = 10; Fold Factor = 379).

Worker Margin of Exposure (MOE) Calculations using Animal Oral POD and Engineering Report PDR												
	Animal or Human			Human							Benchmark MOE	Endpoint Type
Exposure Route	POD mg/kg-day	POD Exposure Frequency Days/Wk	POD Route % Absorp	Exposure mg/day Potential Dose Rate (PDR)	Exposure Frequency Days/Wk	Exposure Route % Absorp	Body Weight kg	Exposure mg/kg-day	Structural Alert as % of PMN	Margin of Exposure MOE	30	BMDL
Inhalation	0.010	7	100%	[redacted]	5	100%	80	1.9E+01	100%	**0.0007**	Fold Factor = 40179	
Dermal	0.010	7	100%	[redacted]3	5	100%	80	2.8E+01	100%	**0.0005**		

Risks were identified for workers for systemic effects via inhalation and dermal contract based on quantitative hazard data for analogue (MOE_{Dermal} =0.0005; $MOE_{Inhalation}$= 0.0007; Benchmark MOE = 30; Fold Factor = 40,179).

Skin, eye and respiratory tract corrosion hazards to workers via inhalation and dermal contact were identified based on the hydrogen fluoride hydrolysis product and analogue data. Risks for these endpoints were not quantified due to a lack of dose-response for these hazards.

3.2.2 General Population Calculations

Population Margin of Exposure (MOE) Calculations using Animal Oral POD and Exposure Report ADR											
	Animal or Human			Human						Benchmark MOE	Endpoint Type
Exposure Route	POD mg/kg-day	POD Exposure Frequency Days/Wk	POD Route % Absorp	Exposure mg/kg-day Acute Dose Rate (ADR)	Exposure Frequency Days/Wk	Exposure Route % Absorp	Multiplier for Susceptible Subpopulations	Structural Alert as % of PMN	Margin of Exposure MOE	30	BMDL
Stack Air Inhalation	0 010	7	100%	[redacted]	7	100%	1.0	100%	**427**		
Fugitive Air Inhalation	0 010	7	100%	[redacted]	7	100%	1.0	100%	**216**		

Risks were not identified for the general population for systemic effects via inhalation of stack air or fugitive air based on quantitative hazard data for analogue ($MOE_{Stack\ Air}$= 427; $MOE_{Fugitive\ Air}$= 216; Benchmark MOE = 30).

Population Margin of Exposure (MOE) Calculations using Animal Inhalation POD and Engineering Report PDR											
	Animal or Human POD			Population Exposure						Benchmark MOE	Endpoint Type
Inhalation Exposure Scenario	POD Conc. mg/m^3	POD Period hrs/day	POD Frequency days/wk	Exposure (24-hr conc.) (ug/m3)	Population Exposure Duration Hours/Day	Exposure Frequency Days/Wk	Structural Alert as % of PMN	POD Conc - Duration Correction - $Scenario_{HEC}$ mg/m^3	**Margin of Exposure MOE**	1000	LOAEC
Stack Air Inhalation	25.00	4.00	6	1.3E-01	24.00	7	100%	3.6E+00	**27,473**		

[redacted]

Risks were not identified for the general population for portal-of-entry, liver, kidney, body weight, and neurotoxicity effects via inhalation of stack air based on quantitative hazard data for an incineration product ($MOE_{Stack\ Air}$ = 27,473; Benchmark MOE = 1000).

Skin, eye, and respiratory tract corrosion hazards to the general population are not expected via stack air or fugitive air releases due to dilution of the chemical substance in the media.

Risks were not evaluated for the general population via drinking water, fish ingestion, or ingestion of groundwater impacted by landfill leachate because releases to water and landfill are not expected.

3.2.3 Consumer Calculations

Risks to consumer were not evaluated because consumer uses were not identified as conditions of use.

[redacted]

Appendix A

Exposure Limit Calculations

New Chemical Exposure Limit (NCEL) for Occupational Inhalation Exposures

NCEL Calculation Non-Cancer Endpoint, Rat NOAEL of 0.1 mg/kg-bw/day from the OECD 421 study, liver effects																		
NOAEL (mg/kg/d)		Uncertainty Factor[1] (unitless)		Permissible Daily Dose (mg/kg/d)		Avg Adult BW 80 (♂ & ♀)[2] (kg)		Permissible Amt per Person per Day (mg/d)		NOAEL Route Absorp-tion Factor[3]		Internal Amount per Person per Day (mg/d)		Air vol. inhaled in 8 hr work shift (m^3)		Inhalation Abs. Rate[3]		**NCEL, 8h Time Weighted Avg (mg/m^3)**
0.01	÷	30	=	0.0003333	x	80	=	0.0266667	x	100%	=	0.026667	÷	10	x	100%	=	**0.00267**

Notes:

[1]The UF includes a 10X uncertainty factor (UF) to account for intraspecies extrapolation and a 10X UF for interindividual variability. If the POD is from human data then do not use the interspecies extrapolation UF of 10. If a LOAEL is used instead of a NOAEL then an additional UF of 10 should be used.

[2]USEPA 2011. Exposure factors handbook, final report, EPA/600-R09/052F, 2011, Chapter 8 Body Weight Studies,Table 8-1, Recommended Values for Body Weight http://www.epa.gov/ncea/efh/pdfs/efh-chapter08.pdf

[3]Absorption estimates based on physical/chemical properties